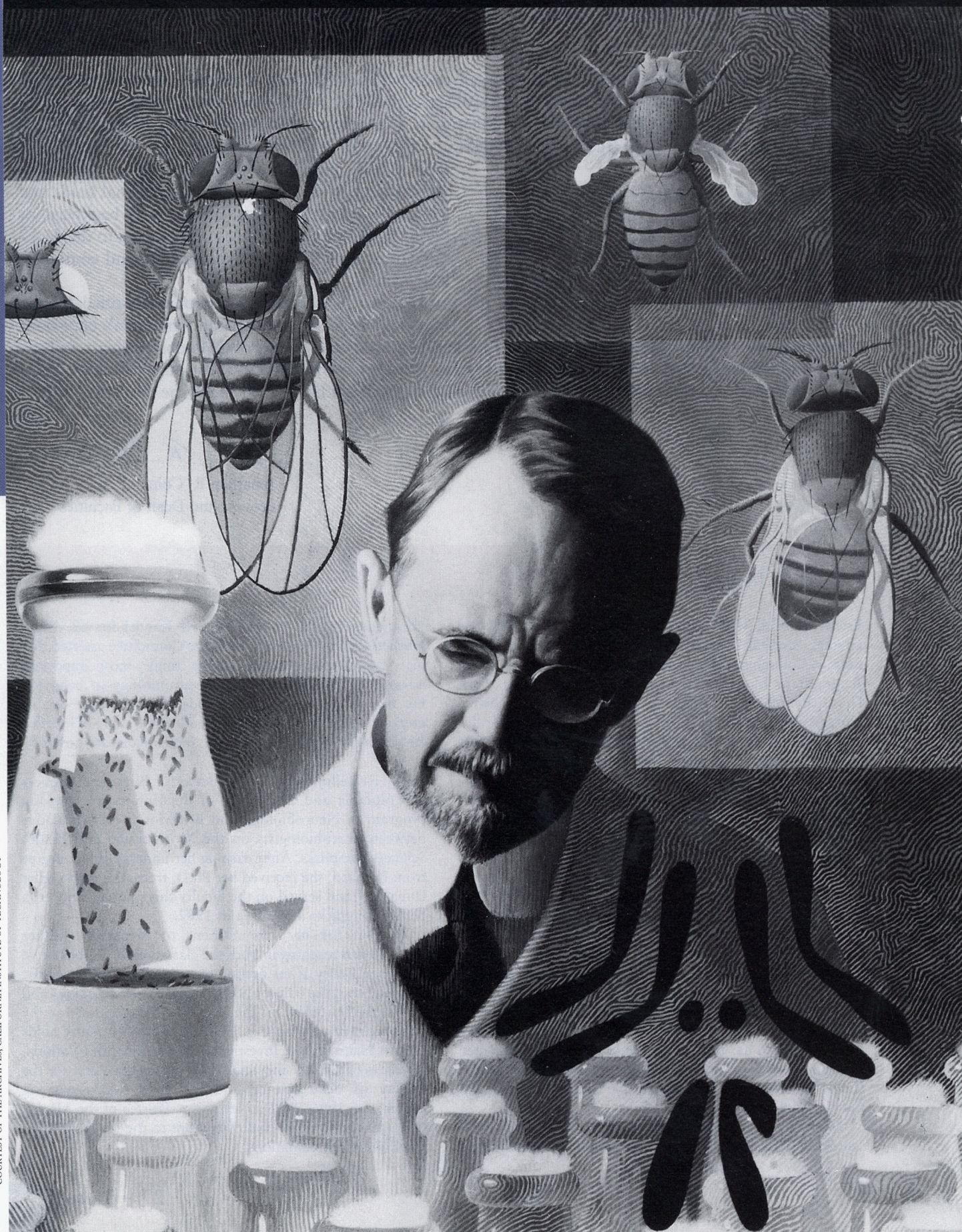
THOMAS HUNT MORGAN



COURTESY OF THE ARCHIVES, CALIFORNIA INSTITUTE OF TECHNOLOGY

AT COLUMBIA UNIVERSITY

Genes, Chromosomes, and the Origins of Modern Biology

Eric R. Kandel

The student of the humanities as well as the intelligent public looks at the history of human thought as a history of abstract ideas. . . . It is true that minds like those of Plato, Thomas Aquinas, Spinoza, Descartes, Hegel and Kant have exercised a strong influence upon the progress of thinking in all spheres, even upon the actual course of historical events. The scientist who looks beyond his specialized work is as fully aware of these historical facts as the humanist. But he is also aware that abstract thinking, remote from, and even antagonistic to the study of nature, leads easily into dogma, taboos and fettering of free thinking because it does not carry its own corrective, the recourse to factual evidence. The scientist, therefore, with all respect for the many facets of the human mind, is more impressed by the revolutions in thinking brought about by great factual discoveries, which by their very nature lead to generalizations which change at once the outlook of many, if not all, lines of thought. Such events are rare. In modern history three are most conspicuous: the explanation of the movements of the celestial bodies by Kepler, Copernicus and Newton; Galileo's experiments inaugurating the age of inductive science, and Darwin's establishment of the theory of evolution on the basis of an overwhelming body of facts. All of them at once evoked the wrath of the vested interests of the mind; all conquered within a generation or two all fields of intellectual endeavor and changed the basic aspects of practically every science, natural or humanistic.

. . . . the rise and development of genetics to mature age is another instance of an all-comprising and all-affecting generalization based upon an overwhelming body of integrated facts, . . . [and] will rank in the history of science with such other great events as mentioned, . . . The basic tenets of genetics have already influenced decisively all parts of biology after what has been only a short span in the history of science; and further that beyond this, many other fields of science have fallen under the spell and we have every reason to believe that genetics is bound to remain in a pivotal position in the future.

—Richard B. Goldschmidt, *The Impact of Genetics Upon Science* (1950)

When future historians turn to examine the major intellectual accomplishments of the twentieth century, they will undoubtedly give a special place to the extraordinary achievements in biology, achievements that have revolutionized our understanding of life's processes and of disease. Important intimations of what was to happen in biology were already apparent in the second half of the nineteenth century. Darwin had delineated the evolution of animal species, Mendel had discovered some basic rules about inheritance, and Weissman, Roux, Driesch, de Vries, and other embryologists were beginning to decipher how an organism develops from a single cell. What was lacking at the end of the nineteenth century, however, was an overarching sense of how these bold advances were related to one another.

The insight that unified these three fields—heredity, evolution, and development—and set biology on the course toward its current success came only at the beginning of the twentieth century. It derived from the discovery that the gene, localized to specific positions on the chromosome, was at once the unit of Mendelian heredity, the driving force for Darwinian evolution, and the control switch for development. This remarkable discovery can be traced directly to one person and to one institution: Thomas Hunt Morgan and Columbia University. Much as Darwin's insights into the evolution of animal species first gave coherence to nineteenth-century biology as a descriptive science, Morgan's findings about genes and their location on chromosomes helped transform biology into an experimental science.

Even more important, Morgan's

COURTESY OF THE ARCHIVES, CALIFORNIA INSTITUTE OF TECHNOLOGY

discoveries made it possible to address a series of questions regarding the function and structure of genes. What is their chemical nature? How do genes duplicate themselves? What goes wrong when genes mutate? How do genes provide the basis for understanding genetic disease? How do genes determine the properties of cells, the development of organisms, and the course of evolution? Answers to some of these questions came directly from Morgan and his students; while other advances were the work of scientists touched by his broader influence. In every case, the discoveries made by these pioneering researchers set the agenda for biology in the twentieth century.

For example, George Beadle, who trained with Morgan and with Morgan's student Alfred Sturtevant '12C '14GSAS, joined Edward L. Tatum to examine how genes determine the properties of the cell. In addressing this problem, they discovered that genes control the synthesis of the cell's proteins, many of which are enzymes. Then Oswald T. Avery '04P&S, another graduate of Columbia, teamed with Maclyn McCarty and Colin MacLeod at the Rockefeller Institute for Medical Research to show that the transforming genetic material is made of DNA. Theodosius Dobzhansky '64HON, a postdoctoral fellow of Morgan's, related genetic mutations to evolutionary change. Hermann J. Muller '10C '11 '16GSAS, another Morgan student, discovered that X-irradiation dramatically increases the rate at which mutations occur, an advance that focused attention on the role of environmentally induced and inherited gene mutations in important diseases ranging from cancer to Huntington's disease and schizophrenia. Joshua Lederberg '44C, an academic grandchild of Morgan, discovered transduction—the ability of viruses to carry exogenous genes into a bacterial cell—the first step on the road to genetic engineering. James D. Watson and Francis Crick next showed that DNA has a double helical conformation, a chemical conformation that immediately led to an understanding of how DNA and genes are replicated. Edward B. Lewis, another academic grandchild of Morgan, used genetics to probe development and found that a special set of genes determines the organization of the body plan. Thus, biology at the beginning of the twenty-first century represents, in good part, the molecular realization of the ideas and way of thinking introduced at the beginning of the twentieth century by Thomas Hunt Morgan at Columbia University.

Morgan and the Mechanisms of Mendelian Heredity

Thomas Hunt Morgan was born in Kentucky in 1866 to a distinguished southern family whose members included Francis Scott Key. Morgan was trained as a developmental biologist, receiving his Ph.D. in 1890 from the Johns Hopkins University for work on the development of sea spiders, a specialized group of invertebrate animals, and in 1891 he accepted a teaching post at Bryn Mawr College.

In 1904 Columbia University announced the establishment of a new chair in experimental zoology and offered it to Morgan. Arriving on campus, he came under the influence of his long-term friend and colleague, the zoology department's chairman, Edwin Wilson, one of the eminent cytologists of his time and a founder of the field of cell biology. Wilson convinced Morgan that the key to understanding development—how one cell, the egg, gives rise to the animal—is to understand heredity, since it provides the means by which the egg and the sperm carry the properties of individuals from one generation to another.

Later findings proved Wilson correct, and we now know that the human genome consists of 46 chromosomes, arranged in 22 pairs of autosomes (not linked to sex), and one pair of sex chromosomes (two X chromosomes in females, one X and one Y chromosome in males). The 100,000 genes in our genome are arranged along the chromosomes in precise order, with each being uniquely identifiable by its location at a characteristic position (*locus*) on a specific chromosome. The two copies of a gene at corresponding loci on each pair of chromosomes are known as *alleles*.

The modern concepts of heredity and the existence of alternative (*allelic*) forms of genes had been discovered in 1865 by Gregor Mendel, a teacher and monk of the Augustinian monastery in Brno, then part of the Austro-Hungarian empire. Mendel carried out breeding experiments with plants, especially garden peas, and identified hereditary traits in them. These traits, later called *factors,* were found by Mendel to account for such features as whether peas were wrinkled or smooth and for the differences between dominant and recessive alleles; he did not know, however, where these traits were located or what they were. Mendel's findings were published in the *Proceedings of the Natural Science Society of Brno* in 1866, only to be ignored until the turn of the century. His work was rediscovered in 1900, just before Morgan arrived at Columbia.

In taking up his own inquiries, Morgan turned from Mendel's plants to the study of animals, but soon found that the rats and mice he was using reproduced so slowly as to be impractical for studying heredity. His search for a more suitable organism led him to *Drosophila melanogaster*, known as the fruit fly because it feeds on decaying fruit. *Drosophila* is small, about 3 mm long, and easy to raise in the laboratory—a thousand can be collected in a one-quart glass milk bottle. Moreover, it is fertile all year long and very prolific, producing a new generation every twelve days, or thirty generations per year. Not only are male and female offspring easy

COURTESY OF THE ARCHIVES, CALIFORNIA INSTITUTE OF TECHNOLOGY

Thomas Hunt Morgan at Columbia, 1917

to distinguish, but embryonic development occurs outside the body, making it a simple matter to study the effects of mutations on development. Finally, *Drosophila* has only four pairs of chromosomes.

Morgan began working seriously with *Drosophila* in 1907, with the intention of breeding many generations of flies, and perhaps producing one that looked different from the rest. In short, he hoped to find an occasional fly that had undergone a *mutation,* sudden change in body form, a phenomenon that had recently been discovered in plants by the Dutch biologist Hugo de Vries. But despite much effort and the breeding of successive generations, Morgan initially failed to detect a single mutation. "Two years work wasted," he lamented to one visitor to his laboratory. "I have been breeding those flies for all that time and I've got nothing out of it."(Harrison, R.G., "Embryology and Its Relations")

Year of Discovery

But Morgan persisted, and in April 1910 he suddenly had a breakthrough. In one of his bottles filled with *Drosophila* was a male fly with white eyes rather than the normal red eyes. Morgan realized the implications of this immediately; the birth of this single spontaneous mutant—*this one male fly with white eyes*—allowed him to begin addressing some key questions in heredity: How did this white eye color originate? What determines eye color?

As the next step, Morgan bred this white-eyed (mutant) male to a red-eyed (wild-type) virgin sister and found that white-colored eyes are inherited in a special way. In the first generation of brother-sister mating, labeled F1, there were only red-eyed offsprings, suggesting that red eye color is *dominant* and that white eye color is *recessive*. To prove this idea Morgan carried out brother-sister matings with the next generation (F2) and found that the offspring followed the expected Mendelian ratio for a recessive trait: three red-eyed flies to every one white-eyed fly. With these experiments Morgan started a tradition, which continues to this day, whereby he named the gene "white" by the result of its mutation. But then came a surprise. He had expected there would be an equal number of males and females with white eyes, but it turned out that all the female flies had red eyes; only males had white eyes, and, even more, only some of them displayed the trait. Morgan realized that white eye color is not only recessive but is also linked in some way to *sex*. The subsequent appearance of two other spontaneous mutations (rudimentary wings and yellow body color) also linked to sex further suggested to Morgan that these three genes might be carried on the same chromosome and that this chromosome is the sex chromosome.

By 1910, it was already known that chromosomes occur in pairs and that

COURTESY OF THE ARCHIVES, CALIFORNIA INSTITUTE OF TECHNOLOGY

A 1918 party in honor of A.H. Sturtevant held in the Chart Room of Schermerhorn Hall. Attending are, clockwise from far left: E.G. Anderson, A. Weinstein, S.C. Dellinger, C.B. Bridges, the "honored guest," a dummy of *Pithecanthropus*, A.J. Muller, T.H. Morgan, F. Lutz (barely visible on the extreme right), O.L. Mohr, A.F. Huettner, Sturtevant, and F. Schrader.

Drosophila had four pairs of chromosomes. Several decades earlier, these thread-shaped structures had been seen under a microscope to be located in the nucleus, but nobody knew their function. Morgan later was to describe them in the following terms: "*The egg of every species of animal or plant carries a definite number of bodies called chromosomes. The sperm carries the same number. Consequently, when the sperm unites with the egg, the fertilized egg will contain the double number of chromosomes. For each chromosome contributed by the sperm there is a corresponding chromosome contributed by the egg, i.e., there are two chromosomes of each kind, which together constitute a pair.*" (Morgan, T.H. et al., *The Mechanism of Mendelian Heredity*)

When Morgan turned to examining the fruit fly's chromosomes under the microscope, he immediately appreciated that not all four pairs of chromosomes were always identical. In particular, whereas female flies had two identical-looking X chromosomes, in the male the X chromosome was paired with a Y chromosome, which looks different and is never present in the female.

Morgan deduced that a male must inherit the X chromosome from his mother and Y from his father, and he immediately spotted a correlation between these sex-linked chromosomes and the segregation of the factors determining eye color. When the mother was homozygous and had two copies of the gene for red eyes, the male offspring invariably had red eyes, even if the father had white eyes. But when the mother had white eyes, the male offspring did too, even if the father's eyes were red. In contrast, a female fly gets one X chromosome from each parent, and if one passed along an X chromosome with a gene for red eyes, the offspring had red eyes because the color is dominant over white. Only when both parents gave her an X chromosome with a gene for white eyes did she display the recessive trait. From these observations, Morgan concluded that the allele-producing eye color must lie on the X chromosome that governs sex. This provided the first correlation between a specific trait and a specific chromosome.

Morgan's initial paper on fruit flies, entitled "Sex Limited Inheritance in Drosophila," was published in *Science* in July 1910. In this and in a subsequent paper published in *Science* in 1911, Morgan outlined his three major findings: (1) that genes must reside on chromosomes; (2) that each gene must reside on a particular chromosome; and (3) that the trait for eye color must reside on the sex chromosome, with the eye-color locus (or white gene) being missing on the Y chromosome and red being dominant on the X chromosome.

These findings formed the heart of Morgan's most important idea: *the chromosomal theory of heredity*. He proposed that each chromosome contains a collection of small units called *genes* (a term he adopted from the Danish physiologist Wilhelm Johannsen who had lectured at Columbia in 1909), with different genes having specific locations along specific chromosomes. Once this idea formed in his mind, Morgan sensed

that the experimental power of the fly would allow him to understand heredity.

A focus on chromosomes and their morphology was not what Morgan had in mind when he started to work on flies. In fact, until he saw the white-eyed mutant and appreciated that its defect acted as if it were part of the X chromosome, he had been skeptical about Mendel's theory of heredity and Mendel's factors. Now that he had seen the possibility that these factors might have a physical reality as genes on chromosomes, Morgan began to view the Mendelian theory in a new light.

A Legacy of Accomplishment

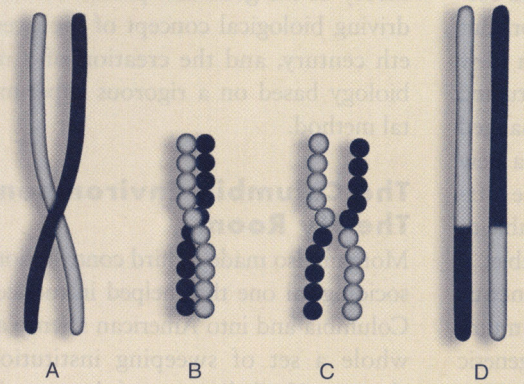
As early as 1911, Morgan had redirected his research in an attempt to provide additional information about the chromosome theory of heredity, and before long he achieved another major conceptual breakthrough. Since chromosomes are contiguous assemblages of genes, those traits (mutations in some of the genes) mapping to one particular chromosome naturally tended to segregate together. But on occasion Morgan noted that these "linked" traits would separate, even while other traits on the same chromosome showed little or even no detectable linkage.

From this evidence, Morgan inferred the process of *chromosome recombination*: he postulated that the two paired chromosomes could "exchange" or "crossover" between each other, and he further proposed that the frequency of recombination is a function of the distance between genes on the chromosome. The nearer two relevant genes lie on a chromosome, the greater their chance of being inherited together, while the farther away they are from each other, the more chance of their being separated by the process of crossing over. In short, Morgan suggested that the strength of linkage between genes depended on the distance between them on the chromosome. (See the figure at right.)

On the basis of these observations, Alfred Henry Sturtevant '12C '14GSAS, then an undergraduate at Columbia College, who was working with Morgan, recognized that the variations in the strength of linkage could be used as a means of mapping genes on chromosomes by determining their relative spatial distances apart. As Sturtevant himself later recalled: "*I suddenly realized that the variations in the strength of linkage already attributed by Morgan to difference in the spatial separation of the gene offered the possibility of determining sequence in the linear dimensions of a chromosome. I went home and spent most of the night (to the neglect of my undergraduate homework) in producing the first chromosome map....*" (Sturtevant, A.H., Unpublished interview with G.E. Allen) The *Morgan* is now the unit of measurement of distances along all chromosomes in fly, mouse, and humans.

A year after Morgan had spotted the white-eyed fly, Sturtevant drew up the first genetic map for the sex-linked genes. A sufficient number of mutations had by then been observed to allow him to express the strength of linkage in units of distance on a chromosome. In fact, the order and spacing that Sturtevant worked out in 1911 are essentially those found on modern maps of the *Drosophila* X chromosome. The profound insight that genes are aligned on the chromosome like beads on a string with specific distances between them eventually produced a conceptual basis for hunting for disease genes through linkage analysis and for mapping whole genomes, such as the human genome. All this was accomplished by a nineteen-year-old Columbia third-year undergraduate by simply skipping one night's homework! Morgan, who was not given to overstatement, later was to call the realization that genes could be precisely mapped in relation to one another on the chromosome as "one of the most amazing developments in the history of biology." (Shine, I. and Wrobel, S., *Thomas Hunt Morgan: Pioneer of Genetics*)

By correlating breeding results with cytological observations of chromosomes under the microscope, Morgan's group rapidly transformed the abstract idea of Mendel's hypothetical factors into the physical reality of particular genes located at specific loci along the length of the chromosome. Initially their maps were quite abstract, since they were based only on the relative positions of genes to one another on the chromosome, as determined by linkage analysis—the sort of



A representation of chromosome recombination, in which paired chromosomes exchange or "cross over." Where black and white rods cross in A, they fuse and unite as shown in D. Details of crossing over are shown in B and C. Morgan's intuition into this process was a step toward creating the first chromosome map, achieved by his student A.H. Sturtevant.

map now called a *recombination* map. But two decades later Calvin Bridges '12C '16GSAS succeeded in developing a second independent map—*a physical one*—showing the exact physical location of a gene on a chromosome. He accomplished this by exploiting an unanticipated advantage of *Drosophila*, which in its larval stages has chromosomes in its salivary glands that Theophilus Painter discovered to be multistranded and gigantic, much larger than the chromosomes of the other cells of the body. These giant chromosomes show a pattern of bands or stripes that divide each chromosome into physical subregions, and Bridges was ultimately able to recognize 1,024 invariant bands on the X chromosome. The development of physical maps proved especially valuable because they allowed a visual presentation of the sequence of genes on the chromosome—a sequence that can only be inferred from the abstract recombination map.

By 1913 Sturtevant contributed yet another major breakthrough with his insight into the existence of different allelic forms, which he saw as alternative states (*alleles*) of the same gene at the same locus. Research on the white-eyed gene clearly revealed that a gene could mutate from one allele to another—from red to white. In some rare instances, a red allele was observed to mutate to a different allele, then to a third and eventually a fourth, with each new allele corresponding to a different eye color. But every time a gene gave rise to a new allele, the mutant form was perpetuated in the offspring and remained unchanged unless—again, in very rare cases—a new mutation occurred in one of the offspring. Thus, Morgan's group was able to show that alleles are remarkably stable!

The low frequency of spontaneous mutation and the perpetuation of mutations that did occur indicated that genetic material is constant. The observation was soon confirmed in many other organisms, from *Drosophila* to man and from bacteria to yeast, offering proof both of inheritance and of the capacity for mutation to allow for evolutionary change in spite of the general constancy of genetic material.

These seminal findings were summarized in 1915 by Morgan and his three Columbia students, Sturtevant, Bridges, and Hermann J. Muller, in *The Mechanism of Mendelian Heredity*, a book that proved to be of historic importance. To begin with, it set forth the physical basis for the new science of genetics. On top of that, the experimental discipline outlined in its pages provided the first experimental basis for a modern biology, transforming it from a descriptive science that relied heavily on morphology. Anatomy, the queen of the biological sciences from the time of the Renaissance to the beginning of the twentieth century, was now replaced by genetics as biology itself emerged as an exact, rigorous, quantitative experimental science that could exist on an equal footing with physics and chemistry.

In recognition of his work on chromosomes, Morgan was awarded the Nobel Prize in Physiology or Medicine in 1933. He shared the prize money with Bridges and Sturtevant. The Nobel Prize recognized Morgan's two fundamental scientific contributions: the development of the chromosome theory of heredity, a theory of the gene that proved to be the driving biological concept of the twentieth century, and the creation of a new biology based on a rigorous experimental method.

The Columbia Environment: The Fly Room

Morgan also made a third contribution, a sociological one that helped introduce at Columbia and into American science as a whole a set of sweeping institutional changes. Until the start of the twentieth century, the leading American research universities—Harvard, Johns Hopkins, Columbia, and Chicago—had all been inspired by the model of the German research university, in which the *Geheimrat*, the great scientific leader, ordered the hierarchy of his subordinates. Morgan, however, based laboratory governance on democratic principles of merit rather than seniority. If one were to ask scientists around the world what is unique about America, they point to the university, and to this day foreign scientists are amazed that students working in a laboratory call professors by their first names.

Morgan surrounded himself with a brilliant group of undergraduate and graduate students. Together they set up the *Drosophila* laboratory in Schermerhorn Hall, Room 613, known worldwide as the *Fly Room*. In retrospect, the Fly Room seems surprisingly small, measuring only 16 x 23 feet and containing eight desks. Yet, it housed a stream of Columbia students as well as foreign visitors and soon received wide recognition, not only for the remarkable quality and clarity of its science but also for the democratic nature of its social interaction. Morgan encouraged the free exchange of ideas in an atmosphere that was at once friendly, yet self-critical.

The atmosphere in the Fly Room was described by Sturtevant, one of the youngest in the group. He wrote:

"This group worked as a unit. Each carried on his own experiments, but each knew exactly what the others were doing, and each new result was freely discussed. There was little attention paid to priority or to the source of new ideas or new interpretations. What mattered was to get ahead with the work. There was much to be done; there were many new ideas to be tested, and many new experimental techniques to be developed. There can have been few times and places in scientific laboratories with such an atmosphere of excitement and with such a record of sustained enthusiasm.

COURTESY OF THE ARCHIVES, CALIFORNIA INSTITUTE OF TECHNOLOGY

Calvin Bridges in the Fly Room, circa 1920

This was due in part to Morgan's own attitude, compounded with enthusiasm combined with a strong critical sense, generosity, open-mindedness, and a remarkable sense of humor." (Sturtevant, A.H., *Thomas Hunt Morgan: Biographical Memoirs*)

Although this idyllic view was not shared by all,* the Fly Room nevertheless characterized science at its best and continues to provide a prototype for how research should be done, at Columbia and elsewhere. In terms of the work conducted there, the science that began at Columbia spread to laboratories all over the world as Morgan, the members of his group, and the scientists they trained helped to shape the course of biology during the decades that followed. Of the people who worked with Morgan directly or who worked with one of his students, five went on to win their own Nobel Prize: Muller, Beadle, Lederberg, and Lewis. Another student, Dobzhansky, went on to place evolution into a modern biological context. Impelled by their achievements, the center of influence in biology shifted from Europe to the United States, making the twentieth century an American Century in biology.

At the same time, the open, critical, yet fully democratic and egalitarian atmosphere that was evident in the Fly Room soon came to characterize the distinctively American atmosphere of university research—an especially significant development as American graduate education increasingly became the model for graduate education throughout the world.

I have benefited from the comments on this essay by Garland Allen, Norman Horowitz, Tom Jessell, Joshua Lederberg, E.B. Lewis, Robert Merton '85HON, Gary Struhl, Andrew Tomlinson, and Harriet Zuckerman '65GSAS.

* As pointed out by Harriet Zuckerman, this view was not shared by Muller, who stood further away from the group than the rest and thought that his own contributions had not been fully recognized: see Zuckerman, 1977, pp. 141–143; see also Allen, 1978, pp. 201–208.

BIBLIOGRAPHY

Allen, G.E. (1978) *Thomas Hunt Morgan: The Man and His Science*. Princeton, NJ: Princeton University Press.

Goldschmidt, R.B. (1950) "The Impact of Genetics Upon Science" in *Genetics in the Twentieth Century, Essays on the Progress of Genetics in Its First Fifty Years* (Ed. L.C. Dunn) pp. 1-23, New York, Macmillan.

Harrison, R.G. (1937) "Embryology and Its Relations," *Science* 85:369–374.

Jaffe, B. (1958) *Men of Science in America: The Story of American Scientists Told Through the Lives and Achievements of Twenty Outstanding Men from Earliest Colonial Times to the Present Day.* Rev. ed., 715 pp. Chapter 16. New York: Simon & Schuster.

Judson, H.F. (1979) *The Eighth Day of Creation: The Makers of the Revolution in Biology*. New York: Simon & Schuster.

Kohler, R. E. (1994) *Lords of the Fly: Drosophila Genetics and the Experimental Life*. Chicago: University of Chicago Press.

Morgan, T.H. et al. (1915) *The Mechanism of Mendelian Heredity*. New York: Holt Rinehart & Winston. Reprinted. Johnson Reprint Corporation with an Introduction by Garland E. Allen, 1978.

Morgan, T.H. (1934) *Embryology and Genetics*. New York: Columbia University Press.

Morgan, T.H. (1938) *The Theory of the Gene*. New Haven: Yale University Press.

Shine, I., and Wrobel, S. (1976) *Thomas Hunt Morgan: Pioneer of Genetics*. Lexington: University of Kentucky Press.

Sturtevant, A.H. (1959) *Thomas Hunt Morgan: Biographical Memoirs*. National Academy of Sciences 33:295.

Sturtevant, A.H. (1965) Unpublished interview with G.E. Allen, Pasadena, Caltech Archives, pg. 28.

Sturtevant, A.H. (1965) *A History of Genetics*. New York: Harper & Row.

Watson, J.D. (1968) *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*. New York: New American Library.

Zuckerman, Harriet (1977) *Scientific Elite: Nobel Laureates in the United States*. New York: Free Press.